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Patricia Gandy 10/18/01  
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## Introduction

There is a growing body of epidemiological literature supporting the positive relationship between a woman's endogenous lifetime hormone exposure and the risk of breast cancer<sup>1-3</sup>. Specifically, early menarche and late menopause are associated with increased risk of breast cancer, and this risk is reduced by surgical oophorectomy in the premenopause. Breast cancer adjuvant treatments often lead to premature menopause, and this may be an important factor in the efficacy of these treatments in younger women<sup>4,5</sup>. However, women who experience premature menopause are at increased risk of earlier cardiovascular disease, as well as premature osteoporosis. Further, numerous epidemiological studies support the benefits of supplemental estrogen therapy in the postmenopause as an effective means of reducing mortality from both cardiovascular disease and osteoporotic fractures. There is uncertainty about how all of these factors play out in breast cancer survivors who have experienced premenopausal disease. Therefore, the primary focus of this cross-sectional study is to examine gonadal function and reproductive health comprehensively in long-term survivors of breast cancer.

## Specific Aims

1. To recruit a sample of breast cancer survivors (BCS) who were 50 years or younger at diagnosis, and were treated initially at the Jonsson Comprehensive Cancer Center at UCLA between 1994 and 1997, to complement a prior study of similar women treated between 1989 and 1994. (Phase One)
2. To recruit additional subjects with identical characteristics treated at Kaiser Permanente West Los Angeles or Kaiser Permanente Sunset between 1989 and 1997. (Phase One)
3. To survey these BCS to determine the effects of past treatment on menstrual history patterns and fertility, as well as past and current menopausal symptoms, and current health-related quality of life. (Phase One)
4. To measure current reproductive hormone status, cardiovascular lipid profiles, body composition and bone mineral density (BMD) in these BCS to assess the late effects of breast cancer treatment on risk factors for coronary artery disease and osteoporotic fractures. (Phase Two)
5. To measure neurocognitive functioning in these BCS to examine whether a relationship exists between various domains of cognitive functioning and type of adjuvant therapy received. (Phase Three)
6. To measure longitudinal BMD in these BCS, 18 months after the initial BMD in Phase Two, to examine if group differences exist among women who received different types of adjuvant therapy. (Phase Four)

## Description of Phases 1, 2, 3 and 4

The study was conducted in four phases. In phase one, the UCLA Medical Center Tumor Registry and the Kaiser Permanente Tumor Registry were used to identify a group of breast cancer survivors who were 50 years or younger at the time of diagnosis and who were disease free at the time of recruitment. Eligible BCS were invited to participate in study and were asked to complete a survey questionnaire that reviewed their menstrual and reproductive history, medication history (including past and current use of contraceptive and non-contraceptive hormones), pregnancy/fertility history, past and current symptoms that may be menopause related, use of alternative therapies, diet and physical activity levels, as well as standardized measures of health-related quality of life. The survey also asked detailed information about each subject's cancer treatment, including type and duration of chemotherapy and hormone therapy received. In addition to analyzing the results from the survey, we will examine the medical and demographic characteristics of breast cancer survivors who participated in comparison with those who refused.

In phase two of the research, all BCS who completed the phase one survey questionnaire were invited to come to UCLA for an in-person visit to complete physical and laboratory studies. These included blood work for evaluation of cardiovascular lipids and gonadal hormones; measurement of blood pressure, height, weight and waist/hip girth; and performance of a bone mineral density test (BMD). The results of the questionnaire data and medical treatment details from phase one, as well as current gonadal hormone levels, will be used to explore the predictors of current health status/health-related quality of life, cardiovascular lipids, and bone mineral density. The analyses planned will examine whether a relationship exists between menstrual patterns after breast cancer and current health-related quality of life, lipid profiles, bone mineral density or body composition. These data will be useful in the management of women who are currently long-term survivors of breast cancer, and can be used to provide supporting pilot data for the design of a prospective longitudinal study examining the impact of breast cancer treatment on the long-term reproductive health of premenopausal women with breast cancer.

Since our original study was designed, we added two new components - a study of neurocognitive functioning (phase three) and a longitudinal follow-up study of bone density (phase four). In phase three of the research, women between 2 and 5 years post-diagnosis who completed phases one and two and who met other eligibility criteria were invited to come to UCLA for an in-person visit to complete a battery of neurocognitive functioning tests. In addition to the neurocognitive tests, we collected saliva samples for cortisol, performed a single blood draw for immune function studies, as well as measured blood pressure and heart rate. Since last year, we discontinued collecting saliva samples, because 1) a preliminary analysis of cortisol levels during and after testing showed no stress effect, and 2) by eliminating saliva collection, we were able to reduce the appointment time from four hours to 2.5 hours, thus reducing subject burden. Since the last reporting period, we have also begun inviting women with no history of breast cancer to come in as control subjects for this phase of the study. The main analysis planned will

examine whether a relationship exists between cognitive functioning and type of adjuvant therapy received (chemotherapy alone; tamoxifen alone; both chemotherapy and tamoxifen; or no therapy). We will also compare neurocognitive functioning between breast cancer survivors and women with no history of breast cancer. The blood measurement is for examination of immune functioning.

In phase four of the research, women who completed phase two are being invited back to receive a follow-up bone mineral density at 18 months after the initial bone density study. We added this phase because of interesting preliminary findings from the cross-sectional evaluation in phase two. We plan to compare group data between the initial and the follow-up BMDs.

### **Progress report on third year of funding**

We applied for and received a no-cost extension because phases three and four of the study are still ongoing. Therefore, this is a progress report rather than a final report.

#### Recruitment and Subject Characteristics

During the past year, we finished recruiting long- and short-term survivors for phase one of the study. Between October 1, 2000 and September 30, 2001, we sent invitation letters to the remaining 142 breast cancer survivors on our tumor registry lists (97 short-term survivors identified by UCLA and 45 short-term survivors identified by Kaiser), for a total of 1084 invitation letters sent since the study began. Of those 1084 initial letters sent, we were able to make subsequent contact with 765 (71%) of the women to ascertain interest in the study. Of these 765 reachable women, 580 (76%) agreed to participate in the study. Among the 580 interested women, 44 (7.5%) women were found to be ineligible, 2 women refused during the telephone screening process, and 404 (70%) women successfully completed the questionnaire.

This year, we also completed data collection for phase two, in which we approached women who completed a questionnaire and who lived in California to come in for an in-person visit, which included a blood draw to measure cholesterol and hormone levels, and a DEXA scan to measure bone mineral density. Between October 1, 2000 and September 30, 2001, we mailed out 102 invitation letters for a total of 392 invitation letters sent for this phase of the study. Of the 375 (96%) invited women who were reachable by phone, 116 (31%) were not interested in participating. Of the remaining 259 women, 15 were deemed ineligible because they were not currently cancer-free; 4 shared data from an unrelated visit; and 240 women completed the appointment.

We made excellent progress on recruitment for phase three this year. Between October 1, 2000, and September 30, 2001, we sent invitation letters to 69 more short-term survivors to come to UCLA for a battery of neurocognitive tests, for a total of 134 women invited since March, 2000. Of these 134, we have been able to make subsequent contact with 119 (89%) women, 70 (59%) of whom were interested in participating. Of

those 70 interested women, 69 have been screened for eligibility; 11 (16%) were found ineligible, 4 (6%) women refused to schedule an appointment, and the remaining 54 were eligible and have already completed their appointments. We have now exhausted the pool of potential breast cancer survivors for phase three, however, we are still in the process of recruiting non-breast cancer controls. Thus far, 17 control subjects have completed their appointments.

Recruitment for phase four also continues to go well. We have thus far sent invitation letters to 77 women who are 18 months past their initial BMD to invite them to come in for a follow-up BMD. Among the 67 (87%) women we were able to make subsequent contact with, only 6 (9%) were not interested. Eight (12%) women were not eligible because they were not currently cancer free. Among the 53 remaining women who were both eligible and interested, 38 have thus far completed their appointment.

#### Additional Data Collection

The recruitment numbers reported for phases one and two above contain only those subjects recruited with DOD funding for this particular study. However, this DOD funding was in fact used to expand on prior data already collected by a similar study that was initiated with NCI funding. Therefore, in addition to the data collected on the subjects described above, we have phase one data on an additional 173 long-term survivors (5-10 years since diagnosis), and biological data on 103 of these women. For all analyses, we will combine data from both the NCI and the DOD studies.

#### Data Analysis

We have now completed data collection for phases one and two of the study. We have questionnaire data from phase one on a total of 577 breast cancer survivors, and bone density and biologic data from phase two on a total of 346 of these women. We have done preliminary analyses on parts of these data for various presentations this and last funding year, but have not yet begun our final analyses.

In this funding year, we wrote and had published a paper entitled "Making Effective Use of Tumor Registries for Cancer Survivorship Research", based on the challenges and successes in recruiting long-term survivors from both a cancer center registry (UCLA) and a community hospital registry (Kaiser) for phase 1 of the study. The paper is attached to this report as Appendix 1.

In May 2001, our co-investigator Dr. Gail Greendale presented an analysis of data from phase two of our study at the 4<sup>th</sup> International Symposium on Women's Health and Menopause in Washington, DC. The abstract and presentation were entitled, "Bone Density in Breast Cancer Survivors." Analyses for this presentation were based on findings from the first 245 completed bone density evaluations. The main analysis compared whole body bone density measurements among four different groups of survivors based on the adjuvant therapy they received for their breast cancer treatment, stratified by menopausal status at time of bone density measurement. The four adjuvant



therapy groups were: No therapy, chemotherapy alone, tamoxifen alone, and chemotherapy plus tamoxifen, and the two menopausal status stratification groups were: pre-menopausal and post-menopausal. The analysis looked at whole body bone density Z scores (which adjust for age and ethnicity) for these breast-cancer survivors, comparing them to the NHANES-III U.S. population based sample. These data were also reported in an editorial by Drs. Ganz and Greendale in the *Journal of Clinical Oncology*<sup>6</sup>.

The results showed that mean whole body BMD scores of pre- and post-menopausal breast cancer survivors who have not received adjuvant therapy are significantly higher than those of age and sex matched population means.

### Key Research Accomplishments

- Collection of questionnaire data from 577 breast cancer survivors, between 2 and 10 years post-diagnosis. These data include information on demographics, menstrual and reproductive history, medication history (including past and current use of contraceptive and non-contraceptive hormones), pregnancy/fertility history, past and current symptoms that may be menopause related, use of alternative therapies, diet and physical activity levels, as well as standardized measures of health-related quality of life. The questionnaire also asks detailed information about each subject's cancer treatment, including type and duration of chemotherapy and hormone therapy received.
- Collection of bone density measurements and biologic data from 346 breast cancer survivors, between 2 and 10 years post-diagnosis. These data include blood work for evaluation of cardiovascular lipids and gonadal hormones; measurement of blood pressure, height, weight and waist/hip girth; and bone mineral density (BMD) measurements at 3 body sites, as well as a whole body measurement.

### Reportable Outcomes

- Manuscript: Pakilit, A.T., Kahn, B.A., Petersen, L., Abraham, L.S., Greendale, G.A., and P.A. Ganz. Making effective use of tumor registries for cancer survivorship research. *Cancer* 92-5: 1305-1314, 2001.
- Abstract and Presentation: G. Greendale, L. Petersen, P.A. Ganz. Bone density in breast cancer survivors. Presented by Dr. Gail Greendale at the 4<sup>th</sup> International Symposium on Women's Health and Menopause, May 19-23, 2001, Washington, DC.
- Editorial: Ganz, P.A. and G.A. Greendale. Menopause and breast cancer: addressing the secondary health effects of adjuvant chemotherapy. *J Clin Oncol* 19:3303-3305, 2001.

- Funding awarded based on work supported by this award: "Neuroimaging Correlates of Cognitive Dysfunction After Breast Cancer Treatment," from the Breast Cancer Research Foundation.
- Funding applied for based on work supported by this award: We have applied for a DOD Idea Award entitled "Innovations in the Evaluation and Detection of Cognitive Dysfunction in Breast Cancer Survivors."

## Conclusion

In this funding year, we completed subject recruitment for phases one and two of the study. A paper about our recruitment process was published in the journal *Cancer*<sup>7</sup>, and one of our investigators, Dr. Gail Greendale, presented research on phase two of our study at the 4<sup>th</sup> International Symposium on Women's Health and Menopause in Washington, DC. In addition, Dr. Ganz and Dr. Greendale published an editorial in the *Journal of Clinical Oncology* about assessing the secondary health effects of adjuvant chemotherapy<sup>6</sup>.

In the upcoming year, we plan to draft a paper describing the phase one sample, looking at differences in menstrual history patterns and fertility, as well as past and current menopausal symptoms, and current health-related quality of life among women in the four adjuvant therapy groups. We also plan to analyze the hormone data from phase two, and analyze the cognitive functioning data from phase three.

Later this month, a co-investigator for phase three, Dr. Steven Castellon, will present "Neurocognitive Performance in Breast Cancer Following Exposure to Adjuvant Systemic Therapy" at the 21<sup>st</sup> Annual Meeting of the National Academy of Neuropsychology in San Francisco, CA.

We will also continue to recruit control subjects for phase three, as well as continue to recruit women for phase four of the study.

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# Making Effective Use of Tumor Registries for Cancer Survivorship Research

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**BACKGROUND.** The growing number of cancer survivors has created an increased need for survivorship research; however, the identification and recruitment of cancer survivors present some challenges. This report describes how two hospital cancer registries were used to recruit a large sample of breast cancer survivors (BCS) for a study examining the late reproductive effects of breast cancer treatments. Limitations and opportunities associated with this type of recruitment strategy are described, and the overall success of recruitment using this approach is presented.

**METHODS.** Tumor registries from a comprehensive cancer center and a community hospital were used to identify BCS who met the study screening criteria. Invitations and response forms were mailed to all potentially eligible women, and those who did not respond by mail also were contacted by telephone. Women who indicated interest and met the study requirements were asked to give written consent, were enrolled in the study, and were sent a self-report questionnaire.

**RESULTS.** Seventy percent of the eligible women ( $n = 733$  women) responded to the mailing. Seventy-seven percent of the 512 respondents indicated a willingness to participate and were sent a questionnaire. Of these, 78% ( $n = 368$  women) completed questionnaires. BCS recruited from the cancer center registry were more likely than those from the community hospital registry to respond to the invitation form ( $P = 0.033$ ) and were more likely to return a completed questionnaire ( $P = 0.001$ ). However, the community hospital provided access to a more ethnically diverse sample of survivors.

**CONCLUSIONS.** The two participating cancer registries were an excellent source for identifying a large sample of long-term BCS, and the different types of registries provided greater sample size and diversity. Although there are some limitations to this approach, including nonresponse of a significant number of BCS, tumor registries represent an important resource for the rapid identification of cancer survivors for research studies. Findings from this study suggest several enhancements for future studies that may increase the yield from registry recruitment. *Cancer* 2001;92:1305-14. © 2001 American Cancer Society.

**KEYWORDS:** cancer registry, recruitment, survivorship, breast carcinoma.

**D**uring the past 5 years, cancer mortality rates have declined in both children and adults.<sup>1</sup> This translates into growing numbers of cancer survivors—individuals surviving many years after initial cancer treatment who are likely to be cured of their initial disease. Nearly 1.4 million Americans will be diagnosed with cancer this year, and approximately 800,000 of them are expected to live for at least 5 more years.<sup>2</sup> Although many survivors have limited sequelae from their cancer treatments, others may suffer late effects of treatment and/or second malignancies that can be a direct consequence of treatment. In addition, there may be long-term psychosocial concerns

associated with cancer survivorship.<sup>3</sup> Recognizing the need for the development of a coordinated program of research to examine the late medical and psychosocial consequences of cancer survivorship, the National Cancer Institute (NCI) recently established an Office of Cancer Survivorship (<http://dccps.nci.nih.gov/ocs>).

According to a 1992 National Health Interview Survey (NHIS), approximately 7.2 million Americans had a cancer diagnosis, excluding skin cancers other than melanoma.<sup>4</sup> However, after individuals are beyond the acute phase of cancer treatment, they often are difficult to identify and recruit for research. Of the NHIS cancer survivor participants, only 14% reported receiving counseling or joining a support group after their diagnoses; 11% reported having contacted cancer organizations, such as the NCI or the American Cancer Society; and 5% reported participating in a research study or clinical trial as part of their treatment. Most cancer survivors did not contact resources outside of their medical team, leaving no large organization through which studies may identify a large pool of potential participants. In the past, researchers have worked with surgeons and oncologists to make contact with cancer survivors; media resources also have been used to recruit more diverse survivor populations. These approaches have been successful, but recruitment is often slow and is laden with ethical considerations of coercion or possible self-selection bias. In the search for a more efficient and representative approach to cancer survivor recruitment, investigators have started to turn to tumor registries.<sup>5,6</sup> Research participant recruitment from cancer registries is a relatively new and undeveloped strategy for the identification of cancer survivors.

During the 20th century, cancer registries evolved primarily as a means of tracking population-based cancer incidence and mortality.<sup>7</sup> Data collection varies by registry, but information, such as type of cancer diagnosed, patient's date of birth, treatment methods, vital status, and contact information, usually are obtained. Use of the tumor registry has expanded the scope of cancer control research and has proved to be a valuable tool in monitoring cancer trends within specific populations.<sup>8</sup> Because cancer registries are a fairly untapped reserve for participant recruitment, there are neither established registry recruitment methods nor information about the efficiency of registries as recruitment tools. This study examines the opportunities and challenges faced when using a tumor registry for recruitment of breast cancer survivors (BCS) for a study designed to assess the late reproductive health effects of breast cancer treatments in younger women. Two cancer registries served as a source for recruitment of participants—one from a

comprehensive cancer center and the other from a community hospital. In this article, we focus on the methods used to identify and recruit potential research participants from the registries, the barriers to complete case identification, and the overall response rate of both registry samples. The purpose of the report is to guide researchers who may wish to use registries for studies of long-term cancer survivors.

## MATERIALS AND METHODS

### Study Setting and Purpose

In 1997, the NCI issued a Request for Proposals (RFP) to provide supplementary funding to Cancer Centers; population-based cancer registries in the Surveillance, Epidemiology and End Results (SEER) Program; and the Cooperative Clinical Trials Groups for studies focusing on cancer survivors between 5 years and 10 years after their diagnosis of cancer. One of the central purposes of the RFP was to determine whether any of these NCI-funded entities could serve readily as a source for the recruitment of long-term cancer survivors. In response to the RFP, we developed a study designed to examine the reproductive late health effects in women diagnosed and treated for breast carcinoma when they were age 50 years or younger (the Cancer and Menopause Study [CAMS]). The first objective of the study was to evaluate the efficacy of recruitment of these BCS from the hospital registry of a comprehensive cancer center. Subsequently, the principal investigator received additional funding for the study from the Department of Defense Breast Cancer Research Program, and the study was expanded to include recruitment from a local community hospital (noncancer center) and to women within 2–5 years after diagnosis. The expansion of the research permitted comparison of two different patient populations and registries as well as BCS at varying times after diagnosis.

The study protocol included completion of a 45-page survey questionnaire booklet that was mailed to women who indicated a willingness to participate (see Hospital Registry Data and Procedures, below). The survey included questions on medical and demographic history, reproductive health, medication use, lifestyle factors (tobacco, alcohol, and exercise), standardized measures of symptoms, and quality of life. Once the survey was completed, geographically accessible participants became eligible for the second phase of the research, which included an in-person visit at the cancer center for assessment of hormone levels, cardiovascular lipids, blood pressure, weight, height and anthropometric measurements, as well as bone densitometry to evaluate potential risk for osteoporosis. For these aspects of the study, descriptive

comparisons were planned for BCS who had received no adjuvant therapy, those who had received tamoxifen alone, those who had received chemotherapy alone, and those who had received chemotherapy and tamoxifen.<sup>9</sup> The data collection from the study is nearing completion. This is our first report on the use of the hospital tumor registry as a recruitment tool, focusing on our results from the recruitment of long-term BCS 5–10 years after diagnosis. All aspects of the research study, including participant recruitment from the hospital registries, the survey questionnaire, and the in-person assessments, were approved by the respective institutional review board (IRB) at each hospital. Written consent was obtained from each participant who enrolled in the study.

### Participant Recruitment

Screening eligibility criteria for the CAMS required identification of women who 1) were diagnosed with their first invasive breast carcinoma or noninvasive breast carcinoma (ductal carcinoma in situ) at the age of 50 years or younger, 2) were alive and currently free of disease, 3) had not had any malignancies prior to the diagnosis obtained from the registry, and 4) were diagnosed between 5 years and 10 years earlier. Recruitment from the cancer center tumor registry and the community hospital tumor registry began in February 1998 and August 1999, respectively, and continued until August 2000. Both registries provided data identifying all patients who met the study criteria and who were diagnosed between 1987 and 1993. Patients with only lobular carcinoma in situ (LCIS) were included in the community hospital registry list and were excluded by the research team prior to mailing invitations to participate in the study. Patients with a foreign address were excluded as well. If a patient appeared on both registry lists, then the research staff made certain that the participant information was not duplicated. Information about diagnosis date, date of birth, race, vital status, address, and phone numbers was obtained for each potentially eligible patient.

Invitation letters were sent to each patient along with a response form and a postage-paid return envelope. The letters were sent on the respective institutional stationery and were signed by the physician at each institution responsible for the study. Physician assent to contact these institutional patients was obtained by the physicians leading the study investigation from each institution; thus, individual physician notification was not required prior to contacting the patients. The response form requested that the patient indicate whether or not she was interested in participating in the study (including a reason for disinterest). It also asked her to provide her date of birth, marital

status, ethnicity, date of cancer diagnosis, address, telephone number, and the most ideal time for contact. For all letters that were returned to sender, we attempted to obtain updated contact information from the cancer center computerized hospital system and from the community hospital registry staff. Invitation letters were remailed to women for whom new addresses were found.

If no mailed response was received after 2 weeks, then a reminder letter was sent asking the woman to return the response form indicating whether or not she was interested in participating. Because there was limited response to the reminder letter alone, the protocol was modified to include a follow-up phone call to all individuals who did not respond to the mailing after 4 weeks. Upon telephone contact or after several phone attempts, these individuals were coded as interested, not interested, or not reachable by phone. Patients who were contacted by telephone were coded in the same way as patients who responded by mail. If available, new addresses and phone numbers were obtained from the cancer center computerized hospital system and the community hospital registry staff for women who were coded as not reachable by phone. The invitation letter was remailed to the updated addresses, and additional follow-up calls were made. If a woman chose to participate during the follow-up call, then the response form demographic information was obtained, and the woman was screened to confirm her eligibility. Women who indicated that they did not wish to participate (on the response form or over the telephone) were asked why they were not interested, and they were coded subsequently into four categories: 1) they were too busy to participate, 2) they felt their experience was too personal or painful to share, 3) they were simply not interested in this research study, or 4) some other reason.

All women who indicated interest in participating by mail were telephoned to complete eligibility screening, to ensure that their disease status had not changed from the status entered in the registry, and to confirm that the registry data were accurate. Patients whose response was obtained by telephone were screened during that initial phone call. Women were asked whether they had been diagnosed with any malignant diseases prior to the registry diagnosis, whether they were diagnosed with LCIS only, and whether they had any active disease at the present time. If a woman responded affirmatively to any of those questions, she was thanked and informed of her ineligibility. Missing data from the response form also were obtained during this call. All eligible women who agreed to participate were sent a questionnaire, two

**TABLE 1**  
Eligibility and Recruitment of Patients from the Registries

Status	Names received					
	Cancer center (n = 367)		Community hospital (n = 382)		Total (n = 749)	
	No.	%	No.	%	No.	%
Not eligible for invitation	11	3.0	5	1.3	16	2.1
Non-US address	6	1.6	0	0.0	6	0.8
LCIS only	3	0.8	1	0.3	4	0.5
No address available	2	0.5	0	0.0	2	0.3
Already on cancer center list	0	0.0	4	1.0	4	0.5
Invitations extended	356	97.0	377	98.7	733	97.9
Not reachable by phone	55	15.0	67	17.5	122	16.3
Return to sender	32	8.7	34	8.9	66	8.8
Deceased	3	0.8	8	2.1	11	1.5
Does not speak English	2	0.5	20	5.2	22	2.9
Received response <sup>a</sup>	264	71.9	248	64.9	512	68.4

LCIS: lobular carcinoma in situ.

<sup>a</sup> P = 0.033. Response varied by registry.

informed consent forms (one form to be signed and returned with the questionnaire and one form for the patients' records), and a postage-paid return envelope.

Participants were asked to complete and return the questionnaire within 2 weeks. Three weeks after each questionnaire was mailed, reminder calls were made to all participants who had an outstanding questionnaire. Multiple phone calls were made until either the questionnaire was returned or the woman indicated unwillingness to complete it. If we were still unable to contact the woman 60 days after the questionnaire mailing, then three additional phone reminders were made. Questionnaires that remained outstanding were considered irretrievable, and no further attempts to contact the participant were made.

#### Hospital Registry Data and Procedures

Each hospital registry was able to provide us with the most current addresses and telephone numbers they had for each of the women deemed eligible based on year of diagnosis and age at the time of diagnosis. Both hospital registries participate in the American College of Surgeons Certification program and practice active follow-up of patients included as analytic cases in the registry. This included annual assessment of vital status, recurrence status, and current treatment. In general, this information was retrieved first through contact with the primary treating physician (or subsequent physicians if known), review of the hospital chart for such information, and, if those sources were not forthcoming, then contact with the

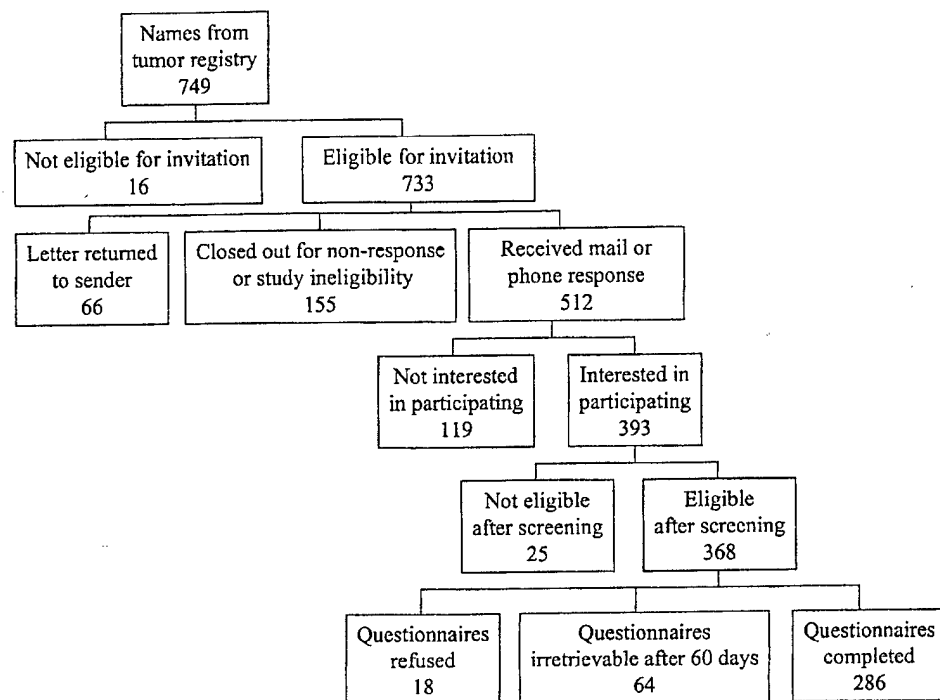
patient or next of kin if known. National death indices are examined periodically to determine vital status. Any time a new contact address is obtained, the registry data base is updated. However, if the patient is lost to follow-up, then there are only limited resources available to pursue further personal contact.

#### Data Analysis

Tumor registry information was received in the form of printed lists of women who met all study criteria. Pertinent information was entered subsequently into a data base using Paradox software (version 5.0; Borland International, Inc. Scotts Valley, CA) and managed using dBase IV software (version 1.5; Borland International, Inc.). Descriptive means and frequencies were run using SAS statistical software (version 6.04; SAS Institute Inc., Cary, NC). *T* tests were used to compare continuous variables, and chi-square tests were used to compare categorical variables between the two hospital registries.

#### RESULTS

We received the names and addresses for 749 women from the two registries, 98% of whom met screening eligibility and were mailed an invitation. Exclusions were ineligible women who could be identified before they were mailed a recruitment letter (see Table 1) and were not due to registry error. Figure 1 provides an overview of the yield from recruitment efforts. Of the 733 letters mailed, we obtained a 68% initial response rate by mail and phone (Table 1). Women who responded by phone were coded identically with women



**FIGURE 1.** Summary of participant eligibility and response.

who responded by mail; therefore, response data were not stratified by method of contact. Reasons for not responding were similar for both the cancer center and the community hospital, but there was a higher response rate from the cancer center sample (71.9% vs. 64.9%;  $P = 0.033$ ). The follow-up invitation phone calls revealed that some women were deceased or did not speak English, making them ineligible for the study, because all materials were in English. The community hospital registry had a greater percentage of non-English speakers, which may have contributed to the lower response rate. The most common reason for lack of response was that women were not reachable by telephone to determine their interest. Most of these women had incorrect or nonworking telephone numbers, so that no messages could be left for potential study participants. Often, the research staff was not able to leave messages for women, because household members were unwilling to take messages or there was no answering machine; this occurred even when telephone numbers were verified.

Data supplied by the tumor registries were used to compare women who were able to be contacted by either mail or phone with women who were not reachable by phone. There were no significant differences between the age, time after diagnosis, or race of those who were contacted (respondents) compared with those who were not contacted (nonresponders) in either the cancer center population or the community hospital population. However, the two registry sam-

ples differed in their response rate at the time of initial contact, and the differences were apparent also in the level of interest in participation in the research. Significantly more women from the cancer center registry were interested in participating in the survey study ( $P = 0.012$ ) (Table 2). Of the respondents from both registries, the primary reasons given for not participating were lack of time or interest in the study. Fewer women refused participation on account of privacy or emotional trauma.

In addition to comparing the demographics of respondents versus nonresponders, we also used tumor registry data to compare the age, time after diagnosis, and race of women who were interested in participating in the study versus those who refused to participate (Table 3). Within each registry, there was no difference in age or time after diagnosis for those who agreed to participate and those who refused. However, in the cancer center sample, there was a significant difference in the ethnicity of participants and refusers. Fewer Asian women agreed to participate than black, Hispanic, or white women. In the community hospital sample, the difference among ethnic groups was not statistically significant. However, Asian women had the lowest rate of participation in the community hospital sample as well. It also should be noted that the community hospital sample was much more diverse ethnically than the cancer center sample.

Of the respondents who were interested in partic-



TABLE 2  
Participation by Registry Site

Status	Responses received					
	Cancer center (n = 264)		Community hospital (n = 248)		Total (n = 512)	
	No.	%	No.	%	No.	%
Interested <sup>a</sup>	215	81.4	178	71.8	393	76.8
Not interested	49	18.6	70	28.2	119	23.2
Too busy	19	7.2	30	12.1	49	9.6
Just not interested	17	6.4	20	8.1	37	7.2
Too personal/painful	7	2.7	10	4.0	17	3.3
Other	6	2.3	10	4.0	16	3.1

<sup>a</sup> P = 0.012. Participation varied by registry site.TABLE 3  
Comparison of Eligible Respondents who Agreed or Refused to Participate

Eligible respondents	Agreed		Refused	
	No.	%	No.	%
Cancer center (n = 251)				
Mean age (yrs)	50.9	—	51.0	—
Mean yrs since diagnosis	7.4	—	7.7	—
Ethnicity <sup>a</sup>				
Asian	10	52.6	9	47.4
Black	16	84.2	3	15.8
Hispanic	10	71.4	4	28.6
White	163	83.2	33	16.8
Other ethnicity	3	100.0	0	0.0
Community hospital (n = 235)				
Mean age (yrs)	51.0	—	50.5	—
Mean yrs since diagnosis	8.0	—	8.3	—
Ethnicity				
Asian	23	59.0	16	41.0
Black	58	68.2	27	31.8
Hispanic	17	68.0	8	32.0
White	64	79.0	17	21.0
Other ethnicity	4	80.0	1	20.0

<sup>a</sup> P = 0.018. Response rate varied by ethnicity.

ipation (n = 393 women), 94% of women were eligible after phone screening. This left 368 women who were enrolled and sent a survey questionnaire. Ultimately, only 78% of the questionnaires were returned (n = 286 women). The completion rate differed by hospital site, with 86% of cancer center women returning the survey and 68% of the community hospital women completing the survey (P = 0.001). For both registries, most of the unreturned questionnaires were coded as irretrievable 60 days after the mailing date, meaning that we were unable to contact the patients during that time to determine a reason for refusal. Therefore, we

considered those questionnaires to be passive refusals rather than outright refusals.

The effort to maximize the sample size by remailing invitations to women who originally were coded as *returned to sender or not reachable by phone* did not prove to be effective. We requested new contact information for 29% of the cancer center letters originally mailed (n = 356 women) and for 50% of the community hospital letters originally mailed (n = 377 women). New addresses were available for only 21% of the cancer center requests (n = 103 women), but 80% of the community hospital requests (n = 189 women) yielded new addresses. We expected a reasonable yield of new participants after mailing a second invitation with these corrected addresses, especially from the community hospital sample. However, only an additional 5% of the unreachable cancer center sample (23% of new addresses) and 20% of the unreachable community hospital sample (25% of new addresses) were interested in participating in the study.

The self-report mailed response forms that were returned to us often contained demographic information that differed from that in found the registry. A comparison was made between the ethnicity reported by the registry and the ethnicity reported by the BCS. Twelve percent of the community hospital respondents reported a race different than that listed in the registry, whereas only 5% of the cancer center respondents reported a different race. This discrepancy between registry and self-reported race differed significantly by registry site (P = 0.009).

There was no significant difference between the education level of the participants from the cancer center and the community hospital (Table 4). However, there were significant differences in racial and economic diversity. The cancer center sample was comprised of predominantly white participants,

TABLE 4  
Ethnicity, Income, and Education of Survey Participants

Status	Survey participants					
	Cancer center (n = 173)		Community hospital (n = 113)		Total (n = 286)	
	No.	%	No.	%	No.	%
Ethnicity <sup>a</sup>						
White	140	80.9	44	38.9	184	64.3
Black	11	6.4	40	35.4	51	17.8
Hispanic	9	5.2	9	8.0	18	6.3
Asian	10	5.8	17	15.0	27	9.4
Other	3	1.7	3	2.7	6	2.1
Total family income <sup>b</sup>						
< \$15K	5	2.9	1	1.0	6	2.1
\$15K-\$30K	10	5.9	6	5.4	16	5.7
\$30K-\$45K	17	9.9	23	20.7	40	14.2
\$45K-\$60K	18	10.5	20	18.0	38	13.5
\$60K-\$75K	20	11.7	19	17.1	39	13.8
\$75K-\$100K	32	18.7	22	19.8	54	19.1
> \$100K	69	40.4	20	18.0	89	31.6
Education level						
High school or less	14	8.1	7	6.2	21	7.3
College or less	80	46.2	65	57.5	145	50.7
Postgraduate degree	79	45.7	41	36.3	120	42.0

<sup>a</sup> P = 0.001. Participant ethnicity varied by registry site.

<sup>b</sup> P = 0.002. Participant income level varied by registry site.

whereas the community hospital sample was more diverse ethnically. Also, 40% of the cancer center participants had a household income of \$100,000 per year or greater, whereas the community hospital participants had more varied household income levels.

## DISCUSSION

The tumor registry is emerging as a multipurpose tool for epidemiology and cancer control research.<sup>5,6,8</sup> For example, cancer incidence within specific geographic areas may be used to identify possible carcinogens.<sup>10,11</sup> The effects of intervention, such as the removal of suspected carcinogens, can be examined by comparing the incidence rates preceding and after the intervention. Other examples of registry use are comparing death rates and treatment data to evaluate trends in treatment effectiveness or matching death certificates to tumor registry entries to assess survival.<sup>8</sup> Also, variations in survival rates can be tracked and compared with parallel screening or treatment patterns to determine positive or negative factors that influence cancer incidence. Most importantly, registries can aid in assessing the size of the cancer problem within certain geographic areas to ensure appropriate distribution of resources and to stimulate new research and clinical care initiatives.<sup>12</sup> The majority of

tumor registries today do not yet have established methods for maintaining current information that can be formatted readily for a variety of purposes.<sup>13</sup> However, registries have the potential to act as the main hub of the cancer control effort.<sup>8,12</sup>

Tumor registries vary in their procedures for identifying and tracking patients. For example, state and regional registries, such as those in the SEER Program, passively receive information from individual hospital registries, where active patient identification and follow-up often occur. Therefore, the state and regional registries are most useful for tracking incidence and mortality rates and frequently are used for retrospective evaluations, because data usually do not become available until several years after the patients are identified. For example, linked data from the SEER Program and the Medicare program<sup>14</sup> have been useful in exploring trends in cancer care among individuals enrolled in the Medicare program. In contrast, hospital registries, especially those participating in the American College of Surgeons Cancer Data Base,<sup>15</sup> more often engage in ongoing follow-up of patients who are identified and entered in the hospital registry. This includes annual follow-up to determine the health status of the patient, including death and disease recurrence. These annual follow-up data can be

collected either from the treating physician, from the medical record, or directly from the patient. In conducting these annual follow-ups, the addresses of the patients usually are updated if the patient has been contacted in the process. Therefore, in the development of the CAMS research program, we chose to examine the feasibility of recruitment of long-term survivors from two hospitals with tumor registries engaged in active patient follow-up, where the chance of locating BCS between 5 years and 10 years after diagnosis was likely.

Hospital tumor registries like those used in this study are common in California, because the state has a long-established state registry (with regional registries that report to it) and state legislation that has made cancer a reportable disease. This legislation makes it possible in California to use the various registries for research purposes if IRB approval of the research is obtained. Each state and community varies in its rules regarding use of registries, and we do not know of a consolidated source for this information. The recent report by Swan et al.<sup>12</sup> on cancer surveillance in the United States describes current national efforts underway to expand the scope of population-based cancer registries throughout the country. We believe that this is one of the first articles to describe the use of hospital tumor registries as a source for the identification of cancer survivors. However, as indicated by the results of our study, neither of these registries had complete and accurate contact information for all of the survivors in their data base, and we had to use alternative strategies to locate as many potential participants as possible. Thus, the quality of such data is likely to vary from registry to registry. In particular, this may be a problem for locating long-term survivors many years after the initial diagnosis and entry into the registry.

Despite these limitations, the tumor registries used in this study proved to be an excellent source of quickly identifiable patients who met the basic eligibility for the study of long-term cancer survivors. In addition, the use of two different hospital settings provided sufficient sample size and diversity. Specifically, the cancer center in this study attracted patients from a large geographic area in southern California—the result of having a highly regarded, comprehensive breast cancer program. Thus, it was a referral center for many affluent women who could travel a substantial distance to receive care at the cancer center. In contrast, the community hospital served a health maintenance organization population in its local catchment area—a diverse, working-class, Los Angeles community. There was considerable value in being able to access two such diverse populations for the

research to be conducted in CAMS. In addition, we were able to compare differences in recruitment and uptake of a survivorship research program using these two separate registry populations.

We found that, as a result of these inherent population differences, there were significant differences in ethnicity and income for those women who ultimately participated in the CAMS research (see Table 4). In addition, we observed that the women who received their treatment at the cancer center were more likely to respond and were more likely to complete participation once they agreed. This may have been due to greater economic resources or interest in research among the cancer center population, but a true comparison cannot be made, because the complete demographics of women who did not participate are unavailable. Although the women from the cancer center were a more responsive population, they were not as diverse ethnically or economically as the women who received their treatment from the community hospital. This diversity was the main benefit of using the community hospital registry, even though the contact information was less current than the cancer center registry data.

The CAMS eligibility criteria required the identification of patients who had received their diagnosis and treatment 5–10 years prior to our attempt to contact them. Therefore, the biggest problem we faced with using tumor registry data was that much of the registry contact information had not been updated since each patient's initial treatment. Although both registries claimed to pursue contact with registry patients annually (either through review of the chart, contact with the treating physician, or the patient directly), many addresses and phone numbers were no longer correct, which resulted in many letters being returned to sender. This significantly decreased the initial response rate and prompted the effort to obtain more recent contact information for a second mailing. New addresses and phone numbers also were requested for all women who were coded as unreachable by phone, even if the letters were not returned to sender. Researchers who choose to use hospital registries for similar purposes in the future should plan to devote extra resources to tracing patients whose contact information may not be up to date. In the case of our two registries, this ranged from 29% in the cancer center sample to 50% in the community hospital sample. It is possible that the patient contact data from the cancer center was updated more frequently, because patients had returned to their home communities for follow-up care, and, thus, their status was not available from the initial treating physician or the chart. This would make personal contact with the patient

more frequent. In contrast, patients at the community hospital may have remained within the same health-care setting, and, thus, their health and vital status could be obtained from the medical record without personal contact.

We were able to use hospital medical information systems in both instances to obtain corrected information for many of our initial mailings that were returned. Although the identification of these corrected addresses improved our final yield somewhat, it was not a very large, making us speculate that patients who were difficult to trace may have had other intervening life priorities (e.g., possible change in job, residence, marital status) that may have limited their interest and time in participating in research studies of this type. Nevertheless, it was our goal to obtain the most representative sample possible, and these patients were pursued.

Resource limitations seem to be most critical in determining how accurate contact information will be in a tumor registry data base. More active follow-up strategies will have to be employed in the future if tumor registries are to be relied on for contact information for survivorship studies.<sup>16</sup> Until there is a more generously funded national surveillance program,<sup>12</sup> researchers will have to take these limitations into account in designing survivorship studies by budgeting appropriately for additional time and resources to trace and locate patients. The current report provides a framework to estimate yield at each step in the process from two different types of hospital registries.

In addition to contact information, other registry data sometimes were inaccurate as well. When receiving response forms, the research staff commonly ran into discrepancies between the information reported by the registry and the information reported by the participants. Specifically, the race recorded in the registry did not match the patient's report in 5% of the cancer center sample and in 12% of the community hospital sample. Both registries obtain race information from provider reports; therefore, provider methods of determining race must be examined to discover the source of inaccuracy. Part of the discrepancy may be due to the fact that the community hospital provided service to a more ethnically diverse population. If provider offices are determining race based on appearance or surname, then race easily can be documented incorrectly for people of mixed ancestry or from interracial marriages. Also, both registries had some differences between registry-reported and participant-reported birth dates.

One of the advantages of using tumor registries for recruitment of survivors is that one can compare some basic information on respondents and nonresponders

(e.g., age, date of diagnosis, disease stage, ethnicity). Other information, such as marital status, income, or education, could only be obtained after contact with potential research participants. For example, it would have been interesting to compare the educational level of women who did not respond to our invitation with those who chose to participate, but this information was not available to us.<sup>17</sup> Other strategies could be used to obtain such data, such as zip code matching with census tract data; however, these efforts were beyond the scope of this study. Based on the similar education levels of the participants from both sites, we cannot infer that education played any role in determining whether or not a woman chose to participate. However, the household income of the cancer center participants was significantly higher than that of the community hospital participants. Therefore, there may be a correlation between socioeconomic status and willingness to participate, in that those who have lower incomes may have less time available to participate in research.

All of the points discussed above address limitations related to data obtained from the registry, but there were also limitations due to the study protocol. One possible improvement for a future study would be to document each call record more stringently. The calls that resulted in participation had an obvious outcome, but those calls that were coded as refusals or unreachable by phone were more ambiguous. Response to the multiple contact phone calls varied greatly. The research staff sometimes recorded whether the refusal was polite or antagonistic, but it was documented inconsistently, because this was not specifically part of the protocol. In retrospect, this information would have been helpful in assessing the response of survivors to registry recruitment. It would be useful in the future to know whether the majority of survivors found the unsolicited contact an invasion of privacy or whether only a few individuals were offended. We can recall only one woman who actively contacted us and wanted to know how we had obtained her name and address. We referred her to the hospital tumor registrar as well as to the information in our recruitment letter that described the state legislation about the use of cancer registries for research. We also sent her copies of the hospital consent for treatment form, which has a statement indicating that, if an individual is diagnosed with cancer while being treated at the hospital, the case is reported to the registry according to state law.

Although these are formal ways of indicating to patients that information about their survivorship status was obtained without a breach of confidentiality on the part of the hospital registry, they may only go

part of the way in informing patients and the public about the value of such research. IRBs struggle with issues of privacy and confidentiality in relation to research; however, direct recruitment by physicians may not necessarily protect potential participants against coercion and may not necessarily increase participation in the research.<sup>18</sup> In our other work using rapid patient ascertainment (identifying patients with cancer for research within a few months of diagnosis) with the regional SEER registry, in accordance with the registry protocol, we immediately report those individuals who express concern about their privacy related to the registry and research. The registry then makes a notation in their record to ensure that those individuals are not contacted again in the future. Standardization of such procedures among registries and researchers may be useful.

Currently, there is substantial public discussion regarding privacy and confidentiality related to medical records, including other data used for surveillance research.<sup>19,20,21</sup> In the CAMS research program, we followed all ethical guidelines associated with contact of patients from the registries and indicated to patients how their information had been obtained. There is some tension about how patients should be notified about such research programs and whether it is better for the research team to contact the patient or to have the treating physician do so.<sup>18</sup> In either circumstance, the patient/survivor may be caught off guard learning that their information was provided for a research study without their explicit permission. For this type of research to go forward and expand, it will be critical for scientists, cancer registrars, and public health officials to publicize more widely the important advances that have been made through the use of such registries and to inform cancer patients more broadly of the existence of these registries. In particular, patients and the public need to be made aware of the important contributions they may make to a variety of kinds of research through these efforts. However, in the end, individuals always have the right not to participate in such research.

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